Remarks

Applicant respectfully requests reconsideration. Claims 104-110 and 112-114 are pending for examination with claim 104 being an independent claim. No new matter has been added.

Rejections under 35 U.S.C. §112

Claims 104-110 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. According to the Examiner "claims 104-110 and 112-114...wherein the genus of oligonucleotides is not claimed in a specific biochemical or molecular structure that could be envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention." Specifically the Examiner has stated that "one skilled in the art can envision a sequence with the claimed structure, but would be unable to determine without further experimentation if the sequence had a function that was considered essential for the claimed genus of oligonucleotide."[1] (Office action page 4).

Applicants have adequately described the genus of molecules including a poly-G motif for use in combination with an antigen for the treatment of cancer. Throughout the specification Applicants teach that the molecules useful according to the methods of the invention are nucleic acids having a poly-G motif. In some preferred embodiments, the poly G motif is at least 4 consecutive Gs. (Page 12) In other preferred embodiments the nucleic acid has a modified nuclease resistant backbone. (Pages 13-14) Examples of numerous poly-G containing nucleic acids are shown in the Tables and throughout the description. All of the structure of this class of compounds (oligonucleotides containing a poly-G motif) is set forth clearly in the description found in the specification. One of skill in the art would recognize the full scope of the class of compounds useful in the claimed method. The description adequately demonstrates Applicant had possession of the full scope of compounds.

[1] Applicants wish to point out that the issue of whether it would require undue experimentation to practice a claimed invention is one of enablement.

It is also stated that "the mere contemplation of the claimed genus in the specification is not sufficient to support the present claimed invention directed to a genus of oligonucleotides comprising four contiguous guanines." It is unclear what is meant by this statement. The specification is not simply a mere contemplation of the claimed genus. The whole specification is directed to the description of this class of compounds and how they function therapeutically. The invention is not a prophetic invention. It is supported by numerous data, described in the application. The specification includes 14 examples describing data set forth in 6 Tables and 15 Figures. The assertion that the invention is a "mere contemplation" is inaccurate and not supported by any evidence presented by the examiner.

Finally, it is concluded that "The skilled artisan cannot envision the detailed structure of a genus of oligonucleotides that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification." (Office Action page 5, emphasis added) Initially, Applicants are not aware of such a requirement for reduction to practice of an invention to be essential to completion of conception. If the Examiner is aware of some legal source for such a conclusion he is respectfully requested to provide that source to Applicants. Additionally, Applicants have taught in the specification that a class of compounds can be used to treat disease such as cancer. Applicants have fully described the structure of the class of compounds, methods for making the class of compounds, methods for administering the class of compounds and the types of disease that could be treated. It is unclear what teachings are missing.

Thus, Applicants have demonstrated possession of a class of compounds (oligonucleotides containing a poly-G motif) which can be used according to the methods of the invention. It is respectfully requested that the rejection be withdrawn.

Claims 104-110 and 112-114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The Examiner has stated that "The instant specification does not specifically teach making and/or using a tumor specific antigen and an oligonucleotides 10-50 nucleotide long comprising a sequence chosen from GGGGG, GAGGG, GGGAG, GTGGG, and GGGTG, wherein the

oligonucleotide does not comprise a CG dinucleotide to treat tumor in a subject." (Office Action page 6). It is unclear where the Examiner derives support for the conclusion that the class of poly-G oligonucleotides is not enabled in the absence of a CG motif. The teachings of the specification are consistent with the data in the examples section. The invention relates to the use of oligonucleotides including poly-G motifs. It is not directed to oligonucleotides having CG dinucleotides.

The Examiner has cited several papers in support of the lack of enablement rejection and in particular in support of the argument that the state of the art at the time of the invention was unpredictable.

In particular, the Examiner has cited Leitner et al, Current Pharmaceutical Design, 2001, 7:1641-67 and Mempel et al. Immunology Letter 89, 2003, 47-57 for supporting the unpredictability of using a Poly-G oligonucleotide to treat a tumor in a vertebrate subject using the claimed method. Applicants disagree.

Leitner et al is a review article on genetic vaccines and DNA adjuvants in cancer. Pages 1641-1655 are directed to DNA vaccines and RNA adjuvants. A discussion of CpG ODN begins on page 1655. Pages 1658-1660 describe the use of CpG ODN in tumor therapies. Applicants were unable to identify a specific teaching in the reference with respect to Poly-G oligonucleotides, as claimed in the current invention. Thus the relevance of the reference to the predictability of the claimed invention is unclear. The Examiner is requested to clarify the relevance of the reference to the rejection.

If the reference is cited for the purpose of establishing that CpG ODN are unpredictable in the treatment of cancer, and that somehow that correlates with Poly-G ODN, Applicants respectfully disagree. Applicants point out that Several Phase I and II studies have been performed in humans to date. For instance, subcutaneous administration of CpG oligonucleotides has been performed in humans for a cancer trial. The data are described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004 (copy enclosed). The results were positive and supported further pursuit of a Phase III trial.

Mempel et al describe a study comparing the effect of oligonucleotide injection into a mouse tumor model. In the study, Mempel et al used 3 oligonucleotides, one containing a single CpG dinucleotide (referred to as CpG ODN), another having a single CpG dinucleotide and poly-G motif

(referred to as a poly-G ODN) and a third having no CpG dinucleotide or poly-G motif (referred to as control). The oligonucleotides were not administered in conjunction with an antigen.

The teachings of Mempel et al are not supportive of the unpredictability of the claimed invention for several reasons. Initially, the Mempel et al oligonucleotides are not administered with an antigen, as required by the pending claims. When the poly-G ODN of the invention are administered with an antigen they produce an antigen specific immune response. Additionally, the oligonucleotides of the claimed invention include a poly-G motif and no CpG dinucleotide. Mempel et al did not test any oligonucleotides that fit within the claimed genus. The results of Mempel et al are difficult to reconcile because Mempel et al included a CpG motif in both test oligonucleotides and then attributed the activity of the CpG ODN to the presence of a CpG dinucleotide. The post-filing teachings contained within the Mempel et al reference are not adequate to demonstrate to one of skill in the art that the claimed invention was unpredictable at the time of the invention.

The Examiner concludes that "the instant specification and the claims coupled with the art of record, at the invention was made, do not provide sufficient guidance and/or evidence to reasonably enable the claimed invention." (Office Action page 8)

As described above, numerous examples and data were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Applicant has addressed the supposed unpredictability associated with the prior art discussed above. Thus, one of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

In response to applicant's arguments in the prior response, the Examiner has provided several remarks. For instance the Examiner has stated "that the fact that the working examples of the invention did not produce positive results in every assay tested does not mean that they are unpredictable because both positive data and negative data are consistent and statistically reliable, the argument is found persuasive because it is not apparent how in vitro results not using the material recited in the instant claims reasonably correlate to using the a genus of tumor specific antigen with the claimed genus of oligonucleotides."

Respectfully, the Examiner has not understood the point of Applicants argument. After the quoted section, Applicants argued that the fact that G-motif ODN prevent lethal shock induced by immunostimulatory DNA (Example 5) but not superantigen- or LPS-induced lethal cytokine syndrome (Example 6), demonstrates the specificity of the mechanism of its action. These examples provide further guidance as to how the invention is to be utilized. The point was that the examples demonstrated the immune stimulating ability of the class of ODNs. Applicant did not argue that the negative data directly helped demonstrate that the class of ODN was useful in treating tumors.

The Examiner also argued that "In response to applicant's argument that Example 7 indicates that G motif ODN act as adjuvants for generation of antigen-specific cytotoxic T cells in vivo and CTLs are important in tumor immunity, i.e., for killing tumor cells (See Abbas et al.), the argument is not found persuasive because example 7 discloses an oligonucleotide (PZ2, SEQ ID NO: 2) with IL-2 co-stimulates T cells in vitro. The instant claims do not require IL-2. In view of the prior art of record and lack of teaching in the specification for practicing the claimed method, example 7 is not recognized as correlating to the claimed method. In addition, example 7 is only limited to SEQ ID NO: 2.....In response to applicant's argument that Example 8 displays that G-motif (ODN PZ2) induced NK activity in vivo in experimental mice and NK cells are important in tumor immunity, i.e., for killing of tumor cells (See Abbas et al.), the argument is not found persuasive because the argument is not found persuasive because example 8 discloses an oligonucleotide (PZ2, SEQ ID NO: 2) co-stimulates natural killer cells with IL-2 in vitro. The instant claims do not require IL-2. In view of the prior art of record and lack of teaching in the specification for practicing the claimed method, example 7. In addition, example 7 is only limited to SEQ ID NO: 2 is not recognized as correlating to the claimed method."

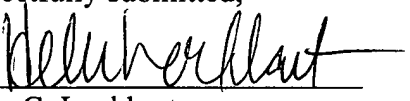
The examples are cumulative. No one example provides 100% of the evidence for supporting the claimed invention. Example 7 and 8 may have been performed with IL-2, but that does not negate it's contribution to the teaching as a whole. The point of the Examples is to demonstrate how this class of ODNs function in stimulating an immune response that is consistent with treating the disease states described in the specification and claimed. There is no legal

requirement that applicant include an example that is exactly demonstrative of every element of the claimed invention. In fact there is no requirement for Applicants to present any data.

In view of the above remarks, applicant believes the pending application is in condition for allowance.

Dated: February 15, 2007

Respectfully submitted,

By 

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[743] TLR9 Agonist Immunomodulator Treatment of Cutaneous T-Cell Lymphoma (CTCL) with CPG7909. Session Type: Oral Session

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CPG 7909 belongs to a new class of chemically defined CpG immunomodulators that target dendritic cell TLR9 receptors inducing IL-12, IFN-gamma, and NK cell function. The rate and durability of response to CPG 7909 was investigated in refractory patients with recurrent or advanced CTCL, who had failed one or more systemic therapies. Dose escalation with weekly sc dosing of patients at 0.08, 0.16, 0.24, or 0.28 mg/kg (3 patients/cohort) for 24 weeks is nearing completion. Additional patients continue to receive treatment at 0.32 (4 patients) or 0.36 mg/kg (12 patients). Clinical response, monitored by Composite Assessment of Index Lesion Disease Severity (CA) and Physician's Global Assessment of Clinical Condition, has been documented. Of 28 patients enrolled, 7 (25%) have achieved objective clinical response, 5 with partial response (PR) and 2 with complete response (CR). Eleven patients have maintained stable disease (SD), while 10 have had progressive disease (PD). Eight patients have completed 24 weeks of treatment (5 SD, 2 PR, 1 CR) with 12-16 weeks of response while on study. Six patients (3 SD, 2 PR,1 CR) are currently ongoing in the study. Three patients (2 PR, 1 SD) continue to receive long term CPG 7909 at 0.12 mg/kg (58 total doses), 0.28 mg/kg (34 total doses) or 0.32 mg/kg (29 total doses) in a follow on protocol. Responses have been maintained up to 46 weeks.
Weekly doses up to 0.36 mg/kg have been well tolerated. Most reported adverse events have been of CTC grade 1 or 2. The most common are dose-related local injection site reactions (erythema, induration, edema, inflammation and pain) and mild or moderate flu-like symptoms (fatigue, rigors, fever, arthralgia). Four patients had CTC grade 3 drug related AEs: one decreased lymphocyte count (0.08 mg/kg), one increased gamma glutamyl transferase (0.16 mg/kg), one decreased absolute polys (0.36 mg/kg) and one fatigue (0.36 mg/kg).
Enrollment in the phase II portion of the study is ongoing and compares results of patients randomized to receive either 10 mg or 25 mg sc weekly for 24 weeks (equating to effective doses seen in dose escalation).

Clinical Response with CPG 7909 - 16 M, 12 F

Dose	N	Disease Stage	CR	PR	SD	PD
0.36 mg/kg	12	IB (7), IIB, III (3), IVA	0	2	6	4

0.32 mg/kg	4	IIA, IIB, IVA (2)	1	0	1	2
0.28 mg/kg	3	IB (2), III	0	1	2	0
0.24 mg/kg	3	IB, IIB (2)	0	1	1	1
0.16 mg/kg	3	IB (2), IIA	1	1	1	0
0.08 mg/kg	3	IB (2), IVA	0	0	0	3
Total	28		7%	18%	39%	36%

Abstract #743 appears in Blood, Volume 104, Issue 11, November 16, 2004
Keywords: Cancer immunotherapy|Phase II|Dendritic cell

Tuesday, December 7, 2004, 08:00 AM

Simultaneous Session: Lymphoma - Therapy with Biologic Agents (8:00 AM-10:00 AM)

[743] TLR9 Agonist Immunomodulator Treatment of Cutaneous T-Cell Lymphoma (CTCL) with CPG7909.
Session Type: Oral Session

Authors: Youn Kim, Michael Girardi, Madeline Duvic, Timothy Kuzel, Alain Rook, Brian Link, Lauren Pinter-Brown, Carol Comerci, Sonja McAuley, Tess Schmalbach

Date/Time: Tuesday, December 7, 2004 - 08:00 AM

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